PATENT COOPERATION TREATY

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/539539

Applicant's or agent's file reference PCT2113FZ904ps	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/41211	International filing date *(day/month/year)* 19.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC C07C65/24		
Applicant MITOKOR, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.07.2004	01.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Romano-Götsch, R Telephone No. +49 89 2399-8874

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/41211

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-36	as originally filed

Claims, Numbers

2-17, 19, 20	as originally filed
1, 18	received on 21.12.2004 with letter of 21.12.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19-20

because:

☒ the said international application, or the said claims Nos. 19-20 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17,19-20
	No:	Claims	18
Inventive step (IS)	Yes:	Claims	1-17,19-20
	No:	Claims	18
Industrial applicability (IA)	Yes:	Claims	1-18 (19-20: no opinion)
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 19-20 are directed to a method of treatment of the animal body, i.e. it contains subject-matter which no International Authority shall be required to examine (Rule 67.1(iv) PCT). Consequently, an opinion in respect to the industrial applicability of said claims has not been established.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The present application does not meet the requirements of Art. 33(2) PCT because the subject-matter of new independent claim 18 is not considered novel over D1 (=EP-A-0253666, cited in the search report).

The argumentation of the Applicant in support of the novelty of claim 18 has been thoroughly considered. The IPEA has come however to the conclusion that claim18 is not novel over D1 as explained below.

On p.15 of D1, a mixture containing the compound (14) and zinc oxide is disclosed.

Compound (14) (p.15) falls under the definition of the compound of present claim 18. Zinc oxide is a UV-light absorber commonly used in dermatological compositions as pigment or UV-light protecting agent, and consequently falls under the definition of "pharmaceutically acceptable carrier" (see description p. 17, lines 12-23).

As a result, the composition of D1 falls under the scope of present claim 18, despite the intended use of the composition is different (Art.33(2) PCT).

Turning to claims 1 and 10, the 3,5-bis(p-tolyloxymethyl)salicylic acid disclosed in D1 (p.15, compound (14)) has been excluded from the scope of claim 1 via a disclaimer. Thus, new independent claim 1 and dependent claim 10 are now novel (Art.33(2) PCT).

Inventive Step

The problem to be solved by the application is regarded as the provision of compounds useful in the treatment of diseases associated with altered mithocondrial functions.

The solution proposed in the application consists in the phenyloxymethylsalicylic acid derivatives

described in present claims 1-17, the composition of claim 18 and the method of treatment of claims 19-20.

Since claim 18 lacks of novelty, an inventive step for said claim cannot be acknowledged.

As to the compounds of claims 1-17, they are not rendered obvious by D1 which relates to a completely different technical problem, namely the provision of electron-donating compounds for a heat-sensitive recording material (see p.1, lines 30-48). Thus, an inventive step for claims 1-17 as well as claims 19-20 is acknowledged (Art. 33(3) PCT).

Industrial Applicability

For the assessment of the presently worded claims 19-20 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not regard as industrially applicable claims to the use of a compound in medical treatment, however will allow claims to a known compound for first use in medical treatment and the use of such compound for the manufacture of a medicament for a new medical treatment.

Further Remarks

The term "prodrug" used in claims 1 and 18 is not considered to clearly and unambiguously define the subject-matter for which protection is sought with regard to the chemical structure of the compounds encompasses within said definition (Art.6 PCT).

The man skilled in the art is not in a position to know without an undue burden of experimentation which compounds would satisfy the desired requirements in order to be suitable prodrug. Moreover, different criteria will apply to nearly every individual compound, since suitable "prodrugs" have to be specifically designed for individual compounds.

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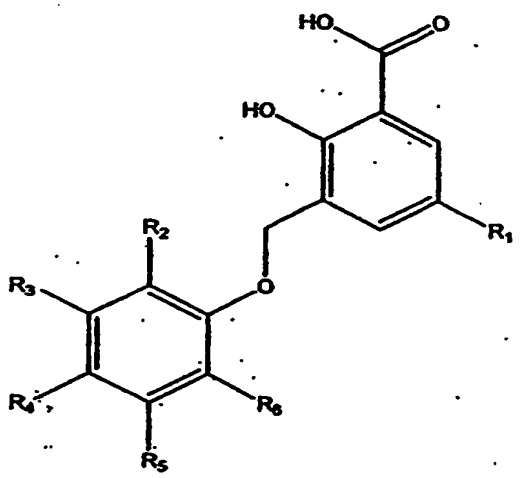
Applicant: MITOKOR INC., et al.
Our Ref.: PCT2113FZ112

Date: December 21, 2004

New claims 1 and 18

1. A compound having the following structure:



or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkoxy, hydroxy, aryl, substituted aryl, -NHC(=O)R', heteroaryl or substituted heteroaryl;

R_2, R_3, R_5 and R_6 are the same or different and independently hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkoxy, hydroxy, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_4 is hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -O-R_7, -C(=O)-R_7, -C(=O)O-R_7, -C(=O)-NH-R_7 or -NHC(=O)R";

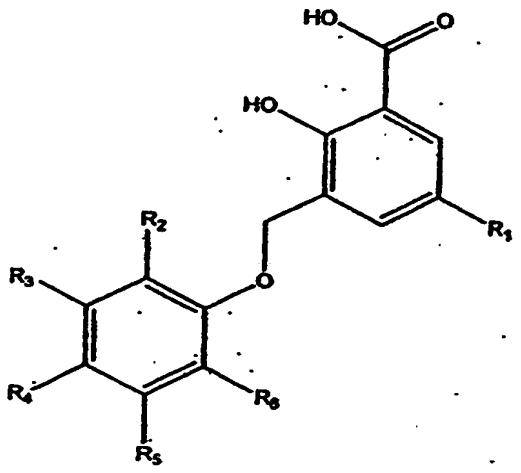
R_7 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl or substituted arylalkyl;

R' and R" are the same or different and independently alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

R_4 and R_5 or R_5 and R_6, taken together with the carbon atoms to which they are attached, optionally form a substituted or unsubstituted homocycle,

with the proviso that the compound is not 3,5-bis(p-tolyloxymethyl)salicylic acid.

18. A composition comprising a compound in combination with a pharmaceutically acceptable carrier, said compound having the following structure:



or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkoxy, hydroxy, aryl, substituted aryl, -NHC(=O)R', heteroaryl or substituted heteroaryl;

R_2, R_3, R_5 and R_6 are the same or different and independently hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkoxy, hydroxy, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_4 is hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl,

substituted heteroarylalkyl, -O-R_7, -C(=O)-R_7, -C(=O)O-R_7, -C(=O)-NH-R_7 or -NHC(=O)R";

R_7 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl or substituted arylalkyl;

R' and R" are the same or different and independently alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

R_4 and R_5 or R_5 and R_6, taken together with the carbon atoms to which they are attached, optionally form a substituted or unsubstituted homocycle.